

ABSTRACT OF THE DISCLOSURE

Hemophilia A is one of the major inherited bleeding disorders caused by a deficiency or abnormality in coagulation factor VIII (FVIII). Hemophiliacs have been treated with whole plasma or purified FVIII concentrates. The risk of transmitting blood-borne viruses and the cost of highly purified FVIII are the major factors that restrict prophylaxis in hemophilia therapy. One of the challenges created by the biotechnology revolution is the development of methods for the economical production of highly purified proteins in large scales. The present invention provides improved mammary expression cassettes useful for the expression of genes at high levels in the milk of transgenic animals. In particular, the present invention provides recombinant signal peptide sequences derived from a-lactalbumin and aS1-casein milk genes suitable for leading protein secretion in the mammary gland. These gene cassettes are capable of delivering different transgenic constructs which result in the production of full-length or B domain-deleted therapeutic levels of biologically active human FVIII in the transgenic animals in vivo. Within the scope of the invention are also method for producing the transgenic non-human mammal, such as mouse, rat, rabbit, goat, sheep, pig and bovine species, capable of expressing human FVIII, and methods of making milk and methods of identifying protein from the transgenic milk.